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HYPOLIPIDEMIC BICYCLIC DERIVATIVES

Abstract:

The invention concerns compounds of formula (I) wherein: l is an integer of from 1 to 4; m is an integer of from 0 to 2; R is independently selected from hydrogen, halogen, nitro, hydroxy, phenylalkoxy, C1-4 alkoxy, C1-6 alkyl, -SO3R", -CO2R" and -O(CH2)pSO3R" wherein p is an integer of from 1 to 4 and R" is hydrogen or C1-6 alkyl, wherein said phenylalkoxy, alkoxy and alkyl groups are optionally substituted by one or more halogen atoms; R<1> is phenyl or pyridyl optionally substituted by one to five groups independently selected from halogen, nitro, hydroxy, phenylalkoxy, C1-4 alkoxy, C1-6 alkyl, -SO3R"', -CO2R"' and -O(CH2)pSO3R"' wherein p is an integer of from 1 to 4 and R"' is hydrogen or C1-6 alkyl, wherein said phenylalkoxy, alkoxy and alkyl groups are optionally substituted by one or more halogen atoms; R<2> is a group independently selected from C1-6 alkyl (including cycloalkyl and cycloalkylalkyl), C2-6 alkenyl, and C2-6 alkynyl which groups are optionally substituted by one or more groups or atoms independently selected from halogen, oxo, C1-4 alkoxy, hydroxy, amino optionally substituted by C1-6 alkyl, thio, and C1-6 alkylthio; R<3> is a group independently selected from C1-6 alkyl (including cycloalkyl and cycloalkylalkyl), C2-6 alkenyl, and C2-6 alkynyl which groups are optionally substituted by one or more groups or atoms independently selected from halogen, oxo, C1-4 alkoxy, hydroxy, amino optionally substituted by C1-6 alkyl, thio, and C1-6 alkylthio; X is CH2 or NH; Y is CH2 or O; and Z is CH or N; provided that when X is CH2, Y is O; and pharmaceutically acceptable derivatives or solvates thereof, to processes for their sy
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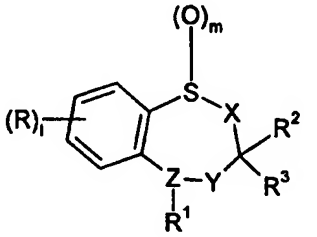
The invention concerns compounds of formula (I) wherein: I is an integer of from 1 to 4; m is an integer of from 0 to 2; R is independently selected from hydrogen, halogen, nitro, hydroxy, phenylalkoxy, C_{1-4} alkoxy, C_{1-6} alkyl, $-SO_3R''$, $-CO_2R''$ and $-O(CH_2)_pSO_3R''$ wherein p is an integer of from 1 to 4 and R'' is hydrogen or C_{1-6} alkyl, wherein said phenylalkoxy, alkoxy and alkyl groups are optionally substituted by one or more halogen atoms; R^1 is phenyl or pyridyl optionally substituted by one to five groups independently selected from halogen, nitro, hydroxy, phenylalkoxy, C_{1-4} alkoxy, C_{1-6} alkyl, $-SO_3R'''$, $-CO_2R'''$ and $-O(CH_2)_pSO_3R'''$ wherein p is an integer of from 1 to 4 and R''' is hydrogen or C_{1-6} alkyl, wherein said phenylalkoxy, alkoxy and alkyl groups are optionally substituted by one or more halogen atoms; R^2 is a group independently selected from C_{1-6} alkyl (including cycloalkyl and cycloalkylalkyl), C_{2-6} alkenyl, and C_{2-6} alkynyl which groups are optionally substituted by one or more groups or atoms independently selected from halogen, oxo, C_{1-4} alkoxy, hydroxy, amino optionally substituted by C_{1-6} alkyl, thio, and C_{1-6} alkylthio; R^3 is a group independently selected from C_{1-6} alkyl (including cycloalkyl and cycloalkylalkyl), C_{2-6} alkenyl, and C_{2-6} alkynyl which groups are optionally substituted by one or more groups or atoms independently selected from halogen, oxo, C_{1-4} alkoxy, hydroxy, amino optionally substituted by C_{1-6} alkyl, thio, and C_{1-6} alkylthio; X is CH_2 or NH; Y is CH_2 or O; and Z is CH or N; provided that when X is CH_2, Y is O; and pharmaceutically acceptable derivatives or solvates thereof, to processes for their synthesis, to pharmaceutical compositions containing them and to their use in medicine, particularly as hypolipidemic agents.



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HYPOLIPIDEMIC BICYCLIC DERIVATIVES

The present invention is concerned with new hypolipidemic compounds, with processes and novel intermediates for their preparation, with pharmaceutical compositions containing them and with their use in medicine, particularly in the prophylaxis and treatment of hyperlipidemic conditions, such as atherosclerosis.

Hyperlipidemic conditions are often associated with elevated plasma concentrations of low density lipoprotein (LDL) cholesterol and very low density lipoprotein (VLDL) cholesterol. Such concentrations can be reduced by decreasing the absorption of bile acids from the intestine. One method by which this may be achieved is to inhibit the bile acid active uptake system in the terminal ileum. Such inhibition stimulates the conversion of cholesterol to bile acid by the liver and the resulting increase in demand for cholesterol produces a corresponding increase in the rate of clearance of LDL and VLDL cholesterol from the blood plasma or serum.

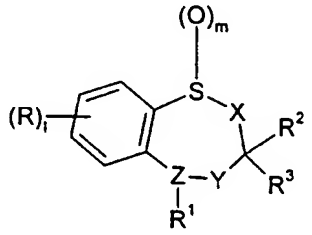
International Patent Application Nos. PCT/GB/9300328 and PCT/GB95/01884 describe hypolipidemic 1,4-benzothiazepine compounds. More recently, International Patent Application No. PCT/GB95/02700 described hypolipidemic 1,5-benzothiazepine compounds and International Patent Application No. PCT/US95/10863 described benzothiepines as being useful in the treatment of hyperlipidemic conditions.

A group of novel compounds has been discovered which also possess hypolipidemic activity. Accordingly, the compounds of the present invention reduce the plasma or serum concentrations of LDL and VLDL cholesterol and in consequence are particularly useful as hypolipidemic agents. By decreasing the concentrations of cholesterol and cholesterol ester in the plasma, the compounds of the present invention retard the build-up of atherosclerotic lesions and reduce the incidence of coronary heart disease-related events. The latter are defined as cardiac events associated with increased concentrations of cholesterol and cholesterol ester in the plasma or serum. Although it is believed that the biological activity of compounds of the present invention resides in their

ability to inhibit bile acid transporter proteins, this mechanistic description is not intended to limit the scope of the invention.

For the purposes of this specification, a hyperlipidemic condition is defined as any condition wherein the total cholesterol concentration (LDL + VLDL) in the plasma or serum is greater than 240mg/dL (6.21mmol/L) (J. Amer. Med. Assn. 256, 20, 2849-2858 (1986)).

Thus, the present invention provides the novel compounds of formula (I)



(I)

wherein :

l is an integer of from 1 to 4;

m is an integer of from 0 to 2;

R is independently selected from hydrogen, halogen, nitro, hydroxy, phenylalkoxy, C_{1-4} alkoxy, C_{1-6} alkyl, $-SO_3R''$, $-CO_2R''$ and $-O(CH_2)_pSO_3R''$ wherein p is an integer of from 1 to 4 and R" is hydrogen or C_{1-6} alkyl, wherein said phenylalkoxy, alkoxy and alkyl groups are optionally substituted by one or more halogen atoms;

R^1 is phenyl or pyridyl optionally substituted by one to five groups independently selected from halogen, nitro, hydroxy, phenylalkoxy, C_{1-4} alkoxy, C_{1-6} alkyl, $-SO_3R'''$, $-CO_2R'''$ and $-O(CH_2)_pSO_3R'''$ wherein p is an integer of from 1 to 4 and R''' is hydrogen or C_{1-6} alkyl, wherein said phenylalkoxy, alkoxy and alkyl groups are optionally substituted by one or more halogen atoms;

R^2 is a group independently selected from C_{1-6} alkyl (including cycloalkyl and cycloalkylalkyl), C_{2-6} alkenyl, and C_{2-6} alkynyl which groups are optionally substituted by one or more groups or atoms independently selected from halogen, oxo, C_{1-4} alkoxy, hydroxy, amino optionally substituted by C_{1-6} alkyl, thio, and C_{1-6} alkylthio;

R^3 is a group independently selected from C_{1-6} alkyl (including cycloalkyl and cycloalkylalkyl), C_{2-6} alkenyl, and C_{2-6} alkynyl which groups are optionally substituted by one or more groups or atoms independently selected from halogen, oxo, C_{1-4} alkoxy, hydroxy, amino optionally substituted by C_{1-6} alkyl, thio, and C_{1-6} alkylthio;
X is CH_2 or NH;
Y is CH_2 or O; and
Z is CH or N;
provided that when X is CH_2, Y is O;
and pharmaceutically acceptable derivatives or solvates thereof.

Referring to formula (I), suitably l is 1 or 2. Preferably l is 2.

Referring to formula (I), suitably m is 0, 1, or 2. Preferably m is 1 or 2. Most preferably, m is 2.

Referring to formula (I), suitably R is hydrogen, halogen, hydroxy, C_{1-4} alkoxy, or a combination thereof. Preferably R is hydrogen, chloro, bromo, hydroxy, methoxy, or a combination thereof. Most preferably, R is hydrogen, bromo, hydroxy, methoxy or a combination thereof. When l is 1 or 2, R is preferably in the 7- and/or 8- position of the molecule.

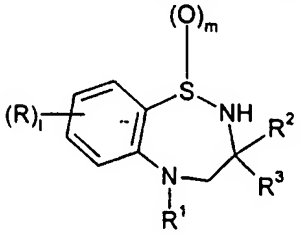
Referring to formula (I), suitably R^1 is an optionally substituted phenyl or pyridyl group. Where R^1 is substituted, substitution is preferably at the 4- and/or 3-position by a group or groups selected from halogen, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, hydroxy, carboxy, or $O(CH_2)_3SO_3H$. Preferably R^1 is unsubstituted phenyl.

Referring to formula (I), suitably R^2 is a C_{1-6} unbranched alkyl group. R^2 is preferably methyl, ethyl or n-propyl. Most preferably R^2 is ethyl.

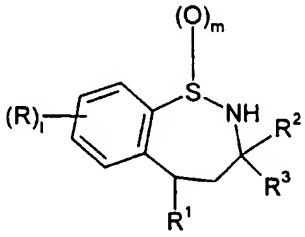
Referring to formula (I), suitably R^3 is a C_{1-6} unbranched alkyl group. Preferably R^3 is ethyl, n-propyl, n-butyl or n-pentyl. Most preferably R^3 is n-butyl.

Referring to formula (I), preferably when X is NH, Y is CH_2 and Z is CH or N.

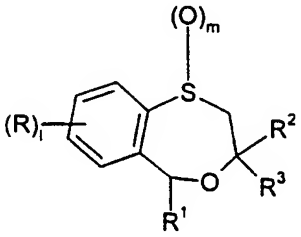
Preferred sub-classes of compounds of formula (I) are represented by the compounds of formulae (Ia), (Ib) and (Ic):



(Ia)



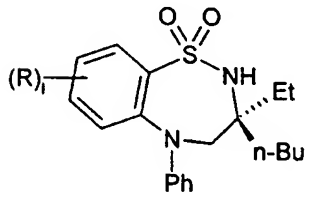
(Ib)



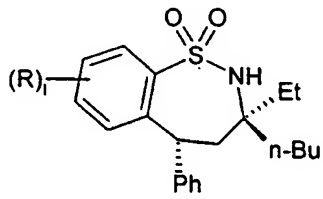
(Ic)

wherein l, m, R, R^1, R^2, and R^3 are as hereinbefore described and, with reference to (Ib) and (Ic), $R^1$and R^3 are in a trans spatial relationship to each other;
and pharmaceutically acceptable derivatives or solvates thereof.

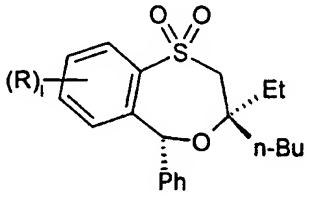
Particularly preferred sub-classes of the compounds of formula (I) are represented by compounds of formulae (Id), (Ie) and (If):



(Id)



(Ie)



(If)

wherein R and l are hereinbefore defined;
and pharmaceutically acceptable derivatives or solvates thereof.

Preferred compounds of the invention include:
3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
3-Butyl-3-ethyl-2,3,4,5-tetrahydro-8-bromo-5-phenyl-1,2,5-benzothiadiazepine 1,1- dioxide;

3-Butyl-3-ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
3-Butyl-3-ethyl-2,3,4,5-tetrahydro-8-hydroxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
3-Butyl-3-Ethyl-2,3,4,5-Tetrahydro-7,8-Dichloro-5-phenyl-1,2,5-Benzothiadiazepine 1,1-dioxide;
3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7,8-dihydroxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-hydroxy-8-methoxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
7-Ethyl-9-phenyl-7-butyl-6,7,8,9-tetrahydro-5-thia-6-aza-benzocycloheptane 5,5-dioxide;
(±)-3-Butyl-3-ethyl-2,3-dihydro-8-methoxy-5-phenyl-5H-1,4-benzothioxepine 1,1-dioxide;
(±)-3,3-Diethyl-2,3-dihydro-8-methoxy-5-phenyl-5H-1,4-benzothioxepine 1,1-dioxide;
(±)-Trans-3-butyl-3-ethyl-2,3-dihydro-8-methoxy-5-phenyl-5H-1,4-benzothioxepine 1,1-dioxide;
3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-bromo-8-hydroxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-methoxy-8-hydroxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
and pharmaceutically acceptable derivatives thereof.

Particularly preferred compounds of the present invention include:
(3S)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
(3S)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-8-bromo-5-phenyl-1,2,5-benzothiadiazepine 1,1- dioxide;
(3S)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
(3S)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-8-hydroxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;

(3S)-3-Butyl-3-Ethyl-2,3,4,5-Tetrahydro-7,8-Dichloro-5-phenyl-1,2,5 Benzothiadiazepine 1,1-dioxide;
(3S)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
(3S)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7,8-dihydroxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
(3S)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-hydroxy-8-methoxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
(7S,9R)-7-Ethyl-9-phenyl-7-butyl-6,7,8,9-tetrahydro-5-thia-6-aza-benzocycloheptane 5,5-dioxide;
(3R,5R)-3-Butyl-3-ethyl-2,3-dihydro-8-methoxy-5-phenyl-5H-1,4-benzothioxepine 1,1-dioxide;
(5R)-3,3-Diethyl-2,3-dihydro-8-methoxy-5-phenyl-5H-1,4-benzothioxepine1,1-dioxide;
(3S)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-bromo-8-hydroxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
(3S)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-methoxy-8-hydroxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
and pharmaceutically acceptable derivatives thereof.

By "a pharmaceutically acceptable derivative" is meant any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of formula (I) or any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof. Pharmaceutically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent, i.e. basic, compounds. Such salts must clearly have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the present invention include those derived from inorganic acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, sulphonic and sulphuric acids, and organic acids, such as acetic, benzenesulphonic, benzoic, citric, ethanesulphonic, fumaric, gluconic, glycollic, isothionic, lactic, lactobionic, maleic, malic, methanesulphonic, succinic, p-toluenesulphonic, tartaric and trifluoroacetic acids. The hydrochloride salt is particularly preferred for medical purposes.

Suitable pharmaceutically acceptable base salts include ammonium salts, alkali metal salts, such as sodium and potassium salts, and alkaline earth salts, such as magnesium and calcium salts.

Salts having a non-pharmaceutically acceptable anion are within the scope of the invention as useful intermediates for the preparation or purification of pharmaceutically acceptable salts and/or for use in non-therapeutic, for example, in vitro, applications.

A further aspect of the present invention is prodrugs of the compounds of the invention. Such prodrugs, which may include pharmaceutically acceptable esters as defined above, can be metabolized in vivo to give a compound according to the invention. These prodrugs may or may not be active in their own right.

The compounds of the present invention can also exist in different polymorphic forms, for example, amorphous and crystalline polymorphic forms. All polymorphic forms of the compounds of the present invention are within the scope of the invention and are a further aspect thereof.

The term "alkyl" as used herein refers, unless otherwise stated, to a monovalent straight or branched chain radical. Likewise, the term "alkoxy" refers to a monovalent straight or branched chain radical attached to the parent molecular moiety through an oxygen atom. The term "phenylalkoxy" refers to a monovalent phenyl group attached to a divalent C_{1-6} alkylene group which is itself attached to the parent molecular moiety through an oxygen atom. All other terms refer to terms of art which are well know to those skilled in the art.

The compounds of formula (I) exist in forms wherein the carbon centers $-CHR^1-$ when Z is CH and $-C(R^2)(R^3)-$ is/are chiral. The present invention includes within its scope each possible optical isomer substantially free, i.e. as associated with less than 5%, of any other optical isomer(s), and mixtures of one or more optical isomers in any proportions, including racemic mixtures.

In those cases where the absolute stereochemistry at -C(R^2)(R^3)- and -CHR^1 has not been determined, the compounds of the invention are defined in terms of the relative positions of the R^2/R^3 and H/R^1 substituents. Thus those compounds wherein the bulkier of the R^2 and R^3 substituents, i.e. the substituent of higher mass, and the R^1 substituent are both located on the same side of the heterocyclic ring are referred to herein as "cis", and those compounds in which they are located on opposite sides of the ring are referred to as "trans". It will be evident to a skilled person that both "cis" and "trans" compounds of the invention can each exist in two enantiomeric forms which are individually designated "(+)-" or "(-)-" according to the direction of rotation of a plane of polarised light when passed through a sample of the compound. Cis or trans compounds of the invention in which the individual enantiomers have not been resolved are referred to herein using the prefix "(+-)-".

All references to "compounds of formula (I)" or "compounds of the present invention" or the like, refer to compound(s) of formula (I) and formulae (Ia)-(If) as described above, and their pharmaceutically acceptable derivatives or solvates.

According to further aspects of the invention, there are also provided:

(a) compounds of formula (I) for use in therapy, particularly in the prophylaxis and treatment of clinical conditions for which a bile acid uptake inhibitor is indicated, for example, a hyperlipidemic condition, such as atherosclerosis;

(b) pharmaceutical compositions comprising a compound of formula (I), at least one pharmaceutically acceptable carrier and, optionally, one or more other physiologically active agents;

(c) the use of a compound of formula (I), optionally, in combination with one or more other physiologically active agents, in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a bile acid uptake inhibitor is indicated, for example, a hyperlipidemic condition, such as atherosclerosis;

(d) a method of inhibiting the absorption of bile acids from the intestine of a mammal, such as a human, which comprises administering an effective bile acid absorption inhibiting amount of a compound of formula (I) to the mammal, optionally, in combination with one or more other physiologically active agents.

(e) a method of reducing the blood plasma or serum concentrations of LDL and VLDL cholesterol in a mammal, such as a human, which comprises administering to the mammal an effective cholesterol reducing amount of a compound of formula (I), optionally, in combination with one or more other physiologically active agents;

(f) a method of reducing the concentrations of cholesterol and cholesterol ester in the blood plasma or serum of a mammal, such as a human, which comprises administering to the mammal an effective cholesterol and cholesterol ester reducing amount of a compound of formula (I), optionally, in combination with one or more other physiologically active agents;

(g) a method of increasing the fecal excretion of bile acids in a mammal, such as a human, which comprises administering to the mammal an effective bile acid fecal excretion increasing amount of a compound of formula (I), optionally, in combination with one or more other physiologically active agents;

(h) a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a bile acid uptake inhibitor is indicated, for example, a hyperlipidemic condition, such as atherosclerosis, which comprises administering to the mammal a therapeutically effective amount of a compound of the formula (I), optionally, in combination with one or more other physiologically active agents;

(i) a method of reducing the incidence of coronary heart disease-related events in a mammal, such as a human, which comprises administering to the mammal an effective coronary heart disease-related events reducing amount of a compound of formula (I), optionally, in combination with one or more other physiologically active agents;

(k) processes for the preparation of compounds of formula (I);

(l) novel chemical intermediates for the preparation of compounds of formula (I); and

(p) A kit comprising a compound of formula (I), optionally, in combination with one or more other physiologically active agents.

Suitable physiologically active agents according to the invention include other hypolipidemic agents such as bile acid sequestering agents, fibric acid derivatives, or HMG-CoA reductase inhibitors (competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase), for example statins, such as pravastatin, lovastatin, fluvastatin, or simvastatin;

The amount of a compound of formula (I) which is required to achieve the desired biological effect will, of course, depend on a number of factors, for example, the specific compound chosen, the use for which it is intended, whether or not it is used in combination with one or more physiologically active agents, the mode of administration and the clinical condition of the recipient. In general, a daily dose is in the range of from 0.001mg to 100mg (typically from 0.01mg to 50mg) per day per kilogram bodyweight, for example, 0.01-10mg/kg/day. Thus orally administrable unit dose formulations, such as tablets or capsules, may contain, for example, from 0.1 to 100mg, typically from 0.1 to 10mg and preferably 0.1 to 5mg. In the case of pharmaceutically acceptable salts, the weights indicated above refer to the weight of the benzothiazepine ion derived from the salt.

For the prophylaxis or treatment of the conditions referred to above, the compounds of formula (I) can be used as the compound per se, but are

preferably presented with an acceptable carrier in the form of a pharmaceutical composition. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the recipient. The carrier can be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compound. Other pharmacologically active substances can also be present including other compounds of formula (I). The pharmaceutical compositions of the invention can be prepared by any of the well known techniques of pharmacy consisting essentially of admixing the components.

When the compound of formula (I) is used in combination with one or more other physiologically active agents as described hereinbefore, the amount of the other physiologically active agents required to achieve the desired biological effect will also depend on a number of factors. The specific dose and dosing schedule will be readily determinable by those skilled in the art. In general, the dose utilized will be the dose approved for medical use in humans.

Pharmaceutical compositions according to the present invention include those suitable for oral, rectal, topical, buccal (e.g. sub-lingual) and parenteral (e.g. subcutaneous, intramuscular, intradermal, or intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular compound of formula (I) which is being used. Enteric-coated and enteric-coated controlled release formulations are also within the scope of the invention. Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methacrylic acid methyl ester. Suitable enteric coated and enteric coated controlled release formulations include tablets and capsules.

Pharmaceutical compositions suitable for oral administration can be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of a compound of formula (I); as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such compositions

can be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and the carrier (which can constitute one or more accessory ingredients). In general, the compositions are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet can be prepared by compressing or molding a powder or granules of the compound, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Molded tablets can be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid diluent. Controlled release tablets can be prepared in a similar manner and with the addition of, for example, hydroxypropylmethyl cellulose.

Enteric-coated tablets or enteric-coated controlled release tablets can be prepared by coating the tablets with an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethyl-cellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

Capsules can be prepared by admixing a compound of formula (I) with, for example, magnesium stearate, pregelantinised starch, sodium starch glycollate, and/or magnesium stearate and filling two-part hard gelatin capsules with the resulting mixture.

Controlled release capsule compositions can be prepared by admixing a compound of formula (I) with, for example, microcrystalline cellulose and/or lactose, extruding using an extruder, then spheronising and drying the extrudate. The dried pellets are coated with a release controlling membrane, for example ethyl cellulose, and filled into two-part, hard gelatin capsules.

Enteric capsule compositions can be prepared by admixing a compound of formula (I) with, for example, microcrystalline cellulose and/or lactose, extruding using an extruder, then spheronising and drying the extrudate. The dried pellets are coated with an enteric membrane, for example cellulose acetate phthalate containing a plasticizer, for example diethyl phthalate and filled into two-part, hard gelatin capsules.

Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of formula (I) in a flavored base, usually sucrose and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Pharmaceutical compositions suitable for parenteral administration conveniently comprise sterile aqueous preparations of a compound of formula (I), preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration can also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations can conveniently be prepared by admixing the compound with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of the active compound.

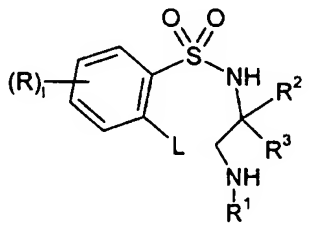
Pharmaceutical compositions suitable for rectal administration are preferably presented as unit-dose suppositories. These can be prepared by admixing a compound of formula (I) with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Pharmaceutical compositions suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which can be used include Vaseline, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound is generally present at a concentration of from 0.1 to 15% w/w of the composition, for example, from 0.5 to 2%.

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound in an optionally buffered, aqueous solution, dissolved and/or dispersed in an adhesive, or dispersed in a polymer. A suitable concentration of the active compound is about 1% to 35%, preferably about 3% to 15%. As one particular possibility, the active compound can be delivered from the patch by electrotransport or iontophoresis, for example, as described in Pharmaceutical Research, 3(6), 318 (1986).

The compounds of the invention can be prepared by conventional methods known to a skilled person or in an analogous manner to processes described in the art and readily available to a skilled person in the art. The starting materials for use in the preparation of the compounds of the invention are known or can be prepared by conventional methods known to a skilled person or in an analogous manner to processes described in the art.

For example, compounds of the formula (I) wherein R, R^1, R^2, R^3, and l are as described hereinbefore, X is NH, Y is CH_2, Z is N, and m is 2 can be prepared by cyclization of compounds of formula (II):



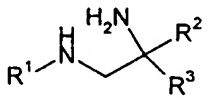
(II)

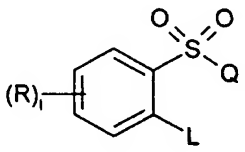
wherein R, R^1, R^2, R^3, and l are as described hereinbefore and L is a suitable leaving group such as halo, for example bromo. For example, the cyclization can be carried out by refluxing a compound of formula (II) in a suitable solvent (for example, N,N-dimethylformamide (DMF)) in the presence of a base (for example potassium carbonate) and optionally with the addition of copper metal.

The compounds of formula (I) wherein m is 0 or 1 can be prepared by reduction of the appropriate compounds of formula (II) wherein m is 2 by methods well known to those skilled in the art or by readily available literature methods.

The compounds of formula (II) as hereinbefore defined as well as each possible optical isomer substantially free, i.e., associated with less than 5% of any other optical isomer(s), and mixtures of one or more optical isomers in any proportions, including racemic mixtures are novel and constitute a further aspect of the present invention.

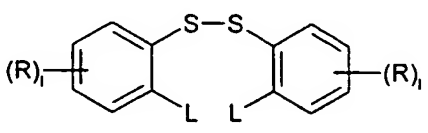
The compounds of formula (II) can be prepared by reacting a compound of formula (III) with a compound of formula (IV):


(III)


(IV)

wherein R, R^1, R^2, R^3, I, and L are as described hereinbefore and Q is a suitable leaving group, such as halo, for example chloro. For example, the reaction can be carried out in a suitable solvent (for example tetrahydrofuran (THF)) in the presence of a base (for example triethylamine) and optionally with the addition of 4-dimethylaminopyridine (DMAP) at a non-extreme temperature (for example -20° C to 100 ° C and preferably 10 ° C to 50° C).

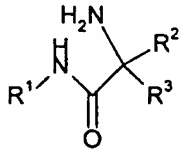
The compounds of formula (IV) are commercially available or can be readily prepared by one skilled in the art following readily available literature procedures. For example, compounds of formula (IV) can be prepared from compounds of formula (IVa):


(IVa)

wherein R and I, are as described hereinbefore and L is halogen, for example, by oxidation of a compound of formula (Iva) with, for example, potassium nitrate followed by halogenation with, for example, a sulfuryl halide such as sulfuryl chloride, in a suitable solvent, for example, acetonitrile at a non-extreme temperature between 0° C and 100° C, preferably room temperature.

The compounds of formula (IVa) can be prepared by reacting the corresponding thiophenol compound of formula (XVI) (described hereinafter) with a halogen, for example bromine, in a suitable solvent such as an organic alcohol, for example methanol, at a non-extreme temperature between 0° C and 100° C, preferably room temperature.

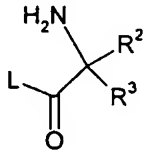
The compounds of formula (III) can be prepared from compounds of formula (V):



(V)

wherein R^1, R^2, R^3 are as described hereinbefore by reduction of the amide carbonyl. For example, the reduction can be carried out with a hydride reducing agent (for example lithium aluminum hydride) in a suitable organic solvent (for example THF) at a non-extreme temperature (for example 0° C to 250° C, and preferably between room temperature and 100° C or the reflux temperature of the solvent).

Compounds of formula (V) can be prepared by condensing compounds of formula (VI):



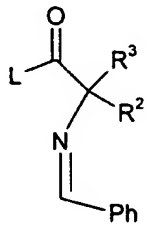
(VI)

R^1—NH_2 (VIa)

wherein R^1, R^2, R^3, and m are as described hereinbefore and L is a suitable leaving group such as alkoxy, for example ethoxy, with the appropriate aniline or aminopyridine of formula (VIa). For example, the compound of formula (VI) can be reacted with a salt of the appropriate aniline (for example the lithio salt) in a suitable solvent (for example THF) at a temperature of -100° C to 50° C and preferably between -78° C and room temperature. Preferably, a lithio salt of the appropriate aniline is reacted with the compound of formula (VI). The lithio salt can be prepared by reaction of the appropriate aniline with an organolithium compound (for example n-butyl lithium) at a temperature of -100° C to 50° C and preferably between -78° C and 0° C.

The appropriate aniline or aminopyridine compounds of formula (VIa) are commercially available or can be readily prepared by one skilled in the art following readily available literature procedures.

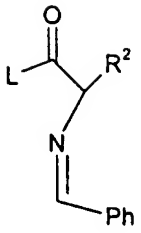
The compounds of formula (VI) can be prepared from the corresponding benzylidine compounds of formula (VII):



(VII)

wherein R^2, R^3, and L are as described hereinbefore, for example, by cleavage of the benzylidine with acid (for example hydrochloric acid) at a non-extreme temperature between 0° C and 50° C, preferably room temperature.

The compounds of formula (VII) can be prepared by reacting an anion of a compound of formula (VIII) with an appropriate alkyl halide (VIIIa):

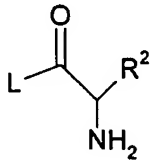


(VIII)

R^3—Q (VIIIa)

wherein R^2 and R^3 are as described hereinbefore with an appropriate compound of formula (VIIIa) wherein Q is a suitable leaving group such as halo, for example iodo. For example, the anion of the compound of formula (VIII) can be generated by reacting the compound of formula (VIII) with a suitable base (for example sodium hydride) in a suitable solvent (for example DMF) at a non-extreme temperature between 0° C and 50° C, preferably room temperature. The appropriate alkyl halide (for example an alkyl iodide) is added and allowed to react at a non-extreme temperature between 0° C and 50° C, preferably room temperature.

The compounds of formula (VIII) can be prepared from compounds of formula (IX):

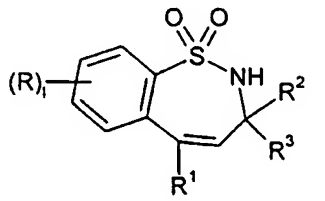


(IX)

wherein R^3 and L are as defined hereinbefore by reaction, for example, with benzaldehyde in the presence of a dehydrating agent (for example magnesium sulfate) and a base (for example triethylamine) in a suitable solvent (for example dichloromethane) at a non-extreme temperature between 0° C and 50° C, preferably room temperature.

Compounds of formula (IX) can be prepared from the corresponding carboxylic acid by methods well known in the art. The corresponding carboxylic acids of compounds of the formula (IX) are commercially available or can be readily prepared by one skilled in the art following readily available literature procedures.

Compounds of formula (I) wherein R, R^1, R^2, R^3, and I are as described hereinbefore, X is NH, Y is CH_2, Z is CH_2 and n is 2 can be prepared by reduction of the olefinic bond of compounds of formula (X):

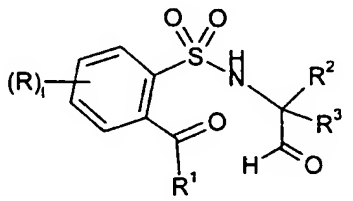


(X)

wherein R, R^1, R^2, R^3, and I are as described hereinbefore. For example, the reduction can be accomplished by catalytic hydrogenation with, for example, hydrogen and a palladium catalyst such as palladium hydroxide or palladium on carbon in a suitable solvent (for example an alcohol such as ethanol), optionally under pressure (for example 10-50 p.s.i.), and at a non-extreme temperature between 0° C and 50° C, preferably room temperature. Alternatively, the reduction can be carried out with a boron compound, for example borane, in a suitable solvent such as THF.

The compounds of formula (X) as hereinbefore defined as well as each possible optical isomer substantially free, i.e., associated with less than 5% of any other optical isomer(s), and mixtures of one or more optical isomers in any proportions, including racemic mixtures are novel and constitute a further aspect of the present invention.

Compounds of formula (X) can be prepared by cyclization of compounds of formula (XI):

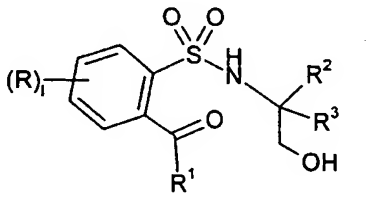


(XI)

wherein R, R^1, R^2, R^3, and I are as described hereinbefore. For example, the cyclization can be carried out with low valent titanium (for example, the low valent titanium can be made in situ from titanium trichloride and a suitable reducing agent such as Zn/Cu or lithium) in a suitable solvent, such as dimethoxyethane, and at a non-extreme temperature between 0° C and 250° C, preferably between 25° C and 100° C, for example at the reflux temperature.

The compounds of formula (XI) as hereinbefore defined as well as each possible optical isomer substantially free, i.e., associated with less than 5% of any other optical isomer(s), and mixtures of one or more optical isomers in any proportions, including racemic mixtures are novel and constitute a further aspect of the present invention.

Compounds of formula (XI) are prepared by oxidation of the corresponding alcohol compounds of formula (XII):

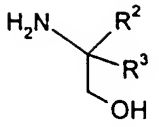


(XII)

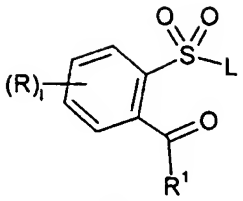
wherein R, R^1, R^2, R^3, and I are as described hereinbefore, by oxidation of the alcohol to an aldehyde, for example with an oxidizing agent such as pyridinium chlorochromate in a suitable solvent, for example methylenechloride, at a non-extreme temperature between 0° C and 50° C, preferably room temperature.

The compounds of formula (XII) as hereinbefore defined as well as each possible optical isomer substantially free, i.e., associated with less than 5% of any other optical isomer(s), and mixtures of one or more optical isomers in any proportions, including racemic mixtures are novel and constitute a further aspect of the present invention.

Compounds of formula (XII) can be prepared by reacting a compound of formula (XIII) with a compound of formula (XIV):



(XIII)

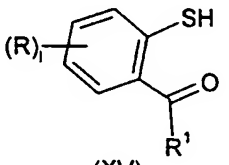


(XIV)

wherein R, R^1, R^2, R^3, and I are as described hereinbefore, and L is a suitable leaving group, for example a halogen, such as chloro. For example, the reaction can be carried out in a suitable solvent, for example THF, optionally in the presence of a base, for example an organic base such as triethylamine, at a non-extreme temperature between 0° C and 100° C, preferably room temperature.

Compounds of formula (XIII) can be prepared by reduction of compounds of formula (VI), described hereinbefore, with, for example, a hydride reducing agent, for example lithium aluminum hydride, in a suitable solvent, for example THF, at a non-extreme temperature between 0° C and 100° C, preferably room temperature.

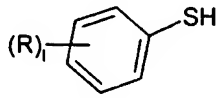
Compounds of formula (XIV) can be prepared from compounds of formula (XV):



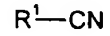
(XV)

wherein R, R^1, and I are as described hereinbefore, for example, by oxidation of a compound of formula (XV) with, for example potassium nitrate and conversion to a sulfonyl halide with a sulfuryl halide such as sulfuryl chloride, in a suitable solvent, for example, acetonitrile, at a non-extreme temperature between 0° C and 100° C, preferably room temperature.

Compounds of formula (XV) can be prepared by reacting the appropriate thiophenol compound of formula (XVI) with the appropriate nitrile compound of formula (XVII):



(XVI)

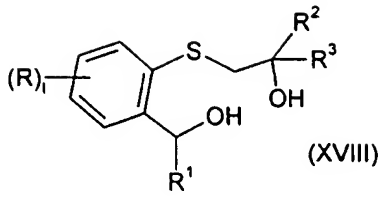


(XVII)

wherein R, R^1, and l are as described hereinbefore followed by hydrolysis to give the thio-keto compound of formula (XV). For example, the reaction can be carried out by first generating the alpha anion of the thiophenol with, for example, an alkyllithium compound such as n-butyllithium in the presence of a co-solvent such as N,N,N',N'-tetramethylethylenediamine (TMEDA) in a suitable solvent, for example, cyclohexane at a non-extreme temperature between 0° C and 100° C, preferably room temperature. The thiophenol anion is then reacted with the appropriate benzonitrile compound of formula (XVII) at a non-extreme temperature between 0° C and 100° C, preferably room temperature. Subsequent hydrolysis, for example with a base such as sodium hydroxide, provides the thio-keto compound of formula (XV).

Compounds of formula (I) wherein X and Z are CH_2, Y is O, and m is 2 can be prepared, for example, by oxidation of the corresponding compound of formula (I) wherein m is 0 with an oxidizing agent, for example 4-methyl-morpholine-N-oxide in the presence of an inorganic oxidizing agent such as osmium tetroxide at a non-extreme temperature between 0° C and 100° C, preferably room temperature. Alternatively, this oxidation may be suitably carried out by reaction with a peroxide, for example hydrogen peroxide or a peroxy acid. The compound of formula (I) wherein m is 1 can be prepared from the corresponding compound where m is 0 using a peroxide as described above.

Compounds of formula (I) wherein X and Z are CH_2, Y is O, and m is 0 can be prepared by cyclization of compounds of formula (XVIII):

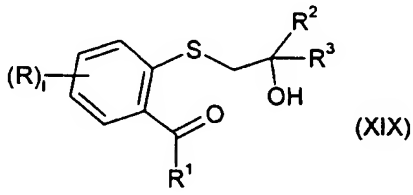


(XVIII)

wherein R, R^1, R^2, R^3, and l are as described hereinbefore, for example, by acid catalyzed hydrolysis with, for example, an ion exchange resin such as Nafion® NR50 beads in a suitable solvent, for example an organic solvent such as toluene at a non-extreme temperature between 0° C and 250° C, preferably at the reflux temperature.

The compounds of formula (XVIII) as hereinbefore defined as well as each possible optical isomer substantially free, i.e., associated with less than 5% of any other optical isomer(s), and mixtures of one or more optical isomers in any proportions, including racemic mixtures are novel and constitute a further aspect of the present invention.

Compounds of formula (XVIII) can be prepared by reduction of the keto-compounds of formula (XIX):



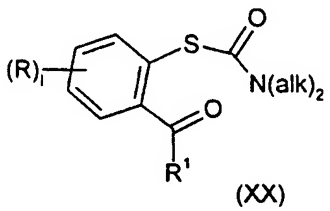
(XIX)

wherein R, R^1, R^2, R^3, and l are as described hereinbefore, for example, with a hydride reducing agent such as sodium borohydride in a suitable solvent such as methanol at a non-extreme temperature between 0° C and 100° C, preferably at room temperature.

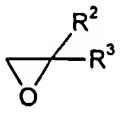
The compounds of formula (XIX) as hereinbefore defined as well as each possible optical isomer substantially free, i.e., associated with less than 5% of any other optical isomer(s), and mixtures of one or more optical isomers in any

proportions, including racemic mixtures are novel and constitute a further aspect of the present invention.

Compounds of formula (XIX) can be prepared by deprotecting a compound of formula (XX):



(XX)

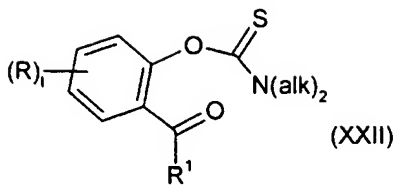


(XXI)

wherein R, R^1, and l are as described hereinbefore and alk is a C_{1-6} alkyl group, and reacting the resulting thiophenol with the appropriately substituted epoxide of formula (XXI) wherein R^2 and R^3 are as described hereinbefore. The deprotection can be carried out with, for example, a base such as sodium hydroxide in a suitable solvent such as THF and/or methanol at a non-extreme temperature between 0° C and 250° C, preferably at about 50 ° C. The resulting thiophenol is reacted with the appropriate epoxide optionally in the presence of a lewis acid catalyst such as tetrabutylammonium fluoride optionally in a suitable solvent at a non-extreme temperature between 0° C and 250° C, preferably at room temperature.

The epoxides of formula (XXI) are commercially available or can be readily prepared by one skilled in the art following readily available literature procedures. For example, the epoxides of formula (XXI) can be prepared by reaction of a sulfur methylide with an appropriate alkyl-ketone at a non-extreme temperature between 0° C and 250° C, preferably at about 50 ° C.

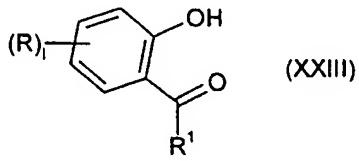
The compounds of formula (XX) can be prepared by rearrangement of the corresponding compounds of formula (XXII):



(XXII)

wherein R, R^1, and alk are as described hereinbefore, for example, by heating at a temperature of about 255° C in a suitable solvent, for example, tetradecane.

The compounds of formula (XXII) can be prepared by reacting a compound of formula (XXIII):



(XXIII)

wherein R, R^1, and l are as described hereinbefore with, for example, dimethylthiocarbamoyl chloride in a suitable solvent such as dioxane in the presence of a base, for example, and organic base such as triethylamine and/or dimethylamino pyridine at a non-extreme temperature between 0° C and 250° C, preferably at the reflux temperature.

Compounds of formula (XXIII) are commercially available or can be readily prepared by one skilled in the art following readily available literature procedures.

Any chiral compounds substantially free of other optical isomers described hereinbefore can be obtained either by chiral synthesis, for example, by use of the appropriate chiral starting material(s), or by resolution of the products obtained from achiral synthesis by standard procedures, for example, by chromatography such as chiral HPLC or by classical resolution with chiral acids or bases. Stereo-isomers and/or geometric isomers substantially free of other isomers can be obtained by standard methods, for example, by chromatography.

Optional conversion of a compound of formula (I), or a compound of formula (I) comprising a basic substituent, to a corresponding acid addition salt may be effected by reaction with a solution of the appropriate acid, for example, one of those recited earlier. Optional conversion of a compound of formula (I) comprising an acidic substituent to a corresponding base salt may be effected by reaction with a solution of the appropriate base, for example, sodium hydroxide. Optional conversion to a physiologically functional derivative, such as an ester, can be carried out by methods known to those skilled in the art or obtainable from the chemical literature.

In addition, compounds of formula (I) may be converted to different compounds of formula (I) by standard methods known or available from the literature to those skilled in the art, for example, by alkylation of a hydroxy group or inter-conversion of a halide group, a hydroxy group, and an alkoxy group.

For a better understanding of the invention, the following Examples are given by way of illustration and are not to be construed in any way as limiting the scope of the invention.

General Procedures- Proton magnetic resonance spectra were recorded at 300 MHz. Mass spectra were recorded under atmospheric pressure chemical ionization (APCI) conditions on an LCMS instrument. Elemental Analyses were performed by Atlantic Microlab, Inc. All anhydrous reactions were performed under a nitrogen atmosphere. TLC plates were Whatman MK6F silica gel 60 plates and were visualized under a UV lamp. Column chromatography was performed with EM Science Silica Gel 60 (230-400 mesh). Reagents were obtained from Aldrich Chemical Co. unless otherwise noted and were used without further purification. Solvents were Aldrich anhydrous grade. Room temperature (RT) means about 25 ^{o}C. The meaning of any abbreviation will be well understood by one skilled in the art when taken in the context of the reaction in which it is used.

Synthetic Example 1

Preparation of 3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide

(a) Ethyl 2-aminobutyrate hydrochloride

A slurry of 2-aminobutyric acid (100g, Aldrich) in absolute ethanol (300 ml) was stirred under nitrogen at 0°C and thionyl chloride (120.8g) was added dropwise. The reaction was stirred overnight at 0°C and then gradually warmed to room temperature. The resulting white slurry was heated under reflux for 3 hours, left to cool for 10 minutes, then poured into chilled diethyl ether (600ml) with stirring. The suspension was filtered and the solid product dried to give the desired product (150g) as a white solid. ^{1}H NMR consistent with proposed structure.

(b) Ethyl 2-benzylideneaminobutyrate

A solution of the product from step (a) (149.6g), magnesium sulfate (74.3g), and triethylamine (246ml) in dichloromethane (1500ml) was stirred at room temperature under nitrogen and benzaldehyde (94.9g, Aldrich) was added dropwise. The mixture was stirred at room temperature for 3 hours and then filtered. The filtrate was concentrated, triturated in diethyl ether, filtered and concentrated to yield the desired product as a yellow oil (174g).^{1}H NMR consistent with the proposed structure.

(c) (±)-Ethyl 2-benzylideneamino-2-ethylhexanoate

Sodium hydride (32.5g, 60% dispersion in oil) and N,N-dimethylformamide (DMF) (700ml) were stirred under nitrogen at room temperature. A solution of the product from step (b) (178.1g) in DMF was added dropwise. After 2 hours stirring at room temperature, a solution of butyl iodide (149.5g) in DMF was added dropwise and the reaction left stirring for a further 2 hours. The reaction was poured into an ice cold mixture of water (560ml), diethyl ether (300ml) and ammonium chloride (120g). The resulting organic layer was dried over potassium carbonate then concentrated to give the desired product as a brown oil (220g).

(d) (±)-Ethyl 2-amino-2-ethylhexanoate

The benzylidene product from step (c) (233.0g) was partitioned between petroleum ether and 10% w/w hydrochloric acid (421ml) and stirred at room

temperature for 2 hours. The aqueous layer was extracted twice with petroleum ether and then chilled with ethyl acetate in an ice-salt bath. Sodium hydroxide pellets were added to the mixture until the aqueous layer was at pH 10. The latter was extracted twice with ethyl acetate and the combined ethyl acetate layers were dried over potassium carbonate, then concentrated and vacuum distilled to give the desired product as a colorless oil. ^{1}H NMR consistent with the proposed structure.

(e) 2-Ethyl-2-amino hexanoic acetanilide

To a stirring solution of aniline (9.3 g) in 200ml THF at -60°C, was added via syringe 200ml 2.5M nBuLi/hexane. After one hour the product from step (d) (18.7g) was added. One hour later the reaction mixture was partitioned between ether and water, extracted 3 times with H_2O, dried, and concentrated to give the desired product as a red oil (23.4g).

^{1}H NMR (DMSO-d6) d 0.85 (t, 3H); 0.91 (t, 3H); 1.00-1.82 (m, 8H); 5.05 (s, 1H); 6.53 (t, 1H); 6.59 (d, 1H); 7.00-7.17 (m, 1H); 7.37 (t, 1H); 7.70 (d, 1H).

(f) 2-Ethyl-N-1-phenyl-hexane-1,2-diamine

230ml of 1M LAH/THF was added to the product from step (e) and warmed to reflux 4 hours. After 16 hours at room temperature the reaction mixture was neutralized in a large beaker with 1N NaOH, extracted with diethyl ether, dried, and concentrated to give the desired product as an amber oil (21.38g).

^{1}H NMR (DMSO-d6) d 0.82 (t, 3H); 0.93 (t, 3H); 1.10-1.50 (m, 8H); 2.83 (d, 2H); 5.08 (m, 2H); 5.22 (m, 1H); 6.53 (m, 1H); 6.59 (d, 1H); 6.65 (d, 1H); 7.05 (t, 1H); 7.11 (t, 1H).

(g) 3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide

To a stirring solution of the product of step (f) (22.0g) in THF (200 ml), triethylamine (10.2g) and DMAP (50mg) was added bromobenzenesulfonyl chloride (Lancaster, 25.5g). After three days the reaction mixture was partitioned between ether and H_2O. The organic layer was dried, concentrated and chromatographed (30% ethyl acetate/hexane) to give an intermediate open-chain product (35g) as a viscous yellow oil. The intermediate was refluxed for 16 h in DMF (200ml) with 22.1g potassium carbonate and 1.0 g copper metal.

Reaction mixture was partitioned between ether and water, extracted 3 times with water, and the ether layer was dried then filtered through Florisil® (activated magnesium silicate). The desired product crystallized as an off-white solid from the ether filtrate (20.36g).

MS Da/e = 359 (MH^+)

Calcd for $C_{20}H_{26}N_2SO_2$ x (0.25 H_2O): C, 66.17; H, 7.36; N, 7.72; S, 8.83.

Found: C, 66.38; H, 7.60; N, 7.60; S, 8.79.

Synthetic Example 2

Preparation of 3-Butyl-3-ethyl-2,3,4,5-tetrahydro-8-bromo-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide

(a) 2,5-Dibromo-N-[1-ethyl-1-(phenylamino-methyl)-butyl]-benzenesulfonamide

To a stirring solution of the product from Synthetic Example 1(f) (6.6g) in 30ml methylene chloride and 30ml 1N aqueous NaOH was added 2, 5-dibromobenzene sulfonyl chloride (Lancaster, 10.03g). After one hour organic layer was dried, concentrated and chromatographed (50% ethyl acetate/hexane) to give the desired product (6.34g).

Calcd for $C_{20}H_{26}Br_2N_2O_2S$: C, 46.34; H, 5.06; Br, 31.84; N, 5.41; S, 6.19.

Found: C, 46.27; H, 5.06; Br, 30.90; N, 5.40; S, 6.21.

(b) 3-Butyl-3-ethyl-2,3,4,5-tetrahydro-8-bromo-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide

This compound was prepared by refluxing the product from step (a) (6.34g) for 16 h in DMF with potassium carbonate and copper metal as outlined for the product from Synthetic Example 1(g). Recrystallization from 50% ethyl acetate/hexane gave the desired product as a white powder (12.3g).

MS Da/e = 438 (MH^+)

Calcd for $C_{20}H_{25}BrN_2O_2S$: C, 54.91; H, 5.76; N, 6.41; Br, 18.27; S, 7.33.

Found: C, 55.07; H, 5.77; N, 6.50; Br, 18.19; S, 7.31.

Synthetic Example 3

Preparation of 3-Butyl-3-ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide

A solution of the product from Synthetic Example 2 (1.00 g) and copper powder (60 mg) in 6 ml 25% sodium methoxide/methanol and 0.1g ethyl acetate was refluxed for 90 minutes. After sixteen hours reaction mixture was partitioned between ethyl acetate and water, extracted 3 times with water, and the ethyl acetate layer filtered through Florisil® and concentrated. Column chromatography (30% ethyl acetate/ hexane) gave the desired product as a white hard foam (0.59g).

^{1}H NMR (DMSO-d6) d 0.80 (m, 6H); 0.92 (m, 1H); 1.08-1.20 (m, 2H); 1.20-1.38 (m, 1H); 1.38-1.50 (m, 2H); 1.50-1.80 (m, 2H); 3.82 (m, 2H); 3.82 (s,3H); 6.90-7.00 (m, 2H); 7.08-7.20 (m, 3H); 7.24-7.38 (m, 4H).

Calcd for $C_{21}H_{28}N_2O_3S$ x (0.5 H_2O): C, 63.45; H, 7.35; N, 7.05; S, 8.07. Found: C, 63.55; H, 7.37; N, 6.92; S, 8.02.

Synthetic Example 4

Preparation of 3-Butyl-3-ethyl-2,3,4,5-tetrahydro-8-hydroxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide

A solution of the product from Synthetic Example 3 (2.80g) in DMF (35 ml) was refluxed for 4 h with the sodium salt of ethanethiol (1.81g). After cooling to RT the solution was transferred to a separatory funnel, adjusted to pH 7, extracted 3 times with ethyl ether, dried over Na_2SO_4 and concentrated. Column chromatography (50% ethyl acetate/hexane) gave the product as an off-white powder (1.68g).

^{1}H NMR (DMSO-d6) d 0.71 (t, 6H); 0.90-1.25 (m, 4H); 1.25-1.41 (m, 2H); 1.41-1.75 (m, 2H); 3.70 (m, 2H); 6.80 (m, 3H); 6.93 (d, 2H); 7.08 (s, 1H); 7.20 (t, 3H); 9.77 (s, 1H).

Calcd for $C_{20}H_{26}N_2O_3S$ x (0.25 H_2O): C, 63.53; H, 7.04; N, 7.41; S, 8.48. Found: C, 63.67; H, 7.09; N, 7.19; S, 8.27.

Synthetic Example 5

Preparation of 3-Butyl-3-Ethyl-2,3,4,5-Tetrahydro-7,8-Dichloro-5-phenyl-1,2,5-Benzothiadiazepine 1,1-dioxide

3,4,6-trichlorobenzenesulfonyl chloride (Lancaster, 8.4g) and the reaction product from Synthetic Example 1(f) (6.6g) were reacted following the procedure for Synthetic Example 1(g) to give the open-chain intermediate, (13.9g).

Cyclization followed by trituration with hexane gave the desired product as a white solid (2.7g).

^{1}H NMR (DMSO-d6) d 0.50 (br m, 6H); 0.80 (m, 3H); 1.08-1.50 (m, 4H); 1.80 (m, 1H); 3.71 (m, 1H); 4.12 (m, 1H); 6.38 (s, 1H); 7.17 (s, 1H); 7.22 (m, 1H); 7.40 (tall m, 4H); 7.87 (s, 1H).

Calcd for $C_{20}H_{24}Cl_2N_2O_2S$: C, 56.20; H, 5.66; N, 6.56; Cl, 16.59; S, 7.50.

Found: C, 56.31; H, 5.62; N, 6.61; Cl, 16.47; S, 7.52.

Synthetic Example 6

Preparation of 3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide

(a) 2-Bromo-4,5-dimethoxybenzenesulfonyl chloride

To a solution of 4-bromoveratrole (21.7g) in methylene chloride (100 ml) at 0°C was added chlorosulfonic acid (46g) . After two hours at RT the reaction mixture was stirred with ice/methylene chloride, extracted with H_2O, dried, and solvent was removed to give the desired product as a viscous colorless oil (16.3g).

^{1}H NMR (DMSO-d6) d 3.72 (s, 3H); 3.74 (s, 3H); 7.03 (s, 1H); 7.23 (s, 1H).

(b) 3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide

This compound was prepared by reacting the product from step (a) with the product from Synthetic Example 1(f) followed by cyclization of the intermediate according to the procedure for Synthetic Example 1(g). Column chromatography yielded the desired product (13.00g).

MS Da/e = 419 (MH^+).

Calcd for $C_{22}H_{30}N_2O_4S$: C, 63.13; H, 7.22; N, 6.69; S, 7.66.

Found: C, 63.05; H, 7.18; N, 6.59; S, 7.72.

Synthetic Examples 7 and 8

Preparation of 3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7,8-dihydroxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide (Synthetic Example 7) and 3-butyl-3-ethyl-2,3,4,5-tetrahydro-7-hydroxy-8-methoxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide (Synthetic Example 8)

A solution of the product from Synthetic Example 6(b) (2.09g) in DMF (35 ml) was refluxed for 4 h with the sodium salt of ethanethiol (1.90g). After cooling to

RT the solution was transferred to a separatory funnel, adjusted to pH 7, extracted 3 times with ethyl ether, dried over Na_2SO_4, concentrated. Column chromatography (50% ethyl acetate/hexane) gave the desired products of Synthetic Example 7, (0.36 g) and Synthetic Example 8 (0.60g).

Example 7 :

MS Da/e = 389 ($M - H^+$)

Calcd for $C_{20}H_{26}N_2O_4S$ x (0.25 EtOAc): C, 61.13; H, 6.84; N, 6.79; S, 7.77.

Found: C, 61.08; H, 6.92; N, 6.50; S, 7.59.

Example 8:

MS Da/e = 405 (MH^+)

Calcd for $C_{21}H_{28}N_2O_4S$ x (0.5 EtOAc): C, 61.57; H, 7.19; N, 6.25; S, 7.15.

Found: C, 61.43; H, 7.14; N, 6.43; S, 7.51.

Synthetic Example 9

Preparation of (±)-Trans-7-ethyl-9-phenyl-7-butyl-6,7,8,9-tetrahydro-5-thia-6-aza-benzocycloheptane-5,5-dioxide

(a) 2-Benzoylbenzenethiol

To a stirring mixture of TMEDA (522g) and cyclohexane (1400ml) was added thiophenol (240g) over a 5 min. period at RT. At -9 °C, n-BuLi (2268g) was added over a 35 min. period. The solution was allowed to come to RT, then after 24 hr. benzonitrile (227.19g) was added over a 16 min period and left overnight. The temperature was reduced to -4 °C. The reaction was quenched with 1200ml water over a 16min period, then diluted with 500 ml 1N NaOH and heated to reflux for one hour under nitrogen. After standing overnight the pH was adjusted to 1. The mixture was extracted with toluene and the organic layer was concentrated to a reddish-brown oil (330.8g). Hexane was added as the oil began to crystallize to a white crystalline solid of the desired product (247.8g).

$C_{13}H_{10}OS$: C, 72.87; H, 4.70; S, 14.96.

Found: C, 72.88; H, 4.71; S, 14.90.

(b) 2-Benzoylbenzenesulfonyl chloride

To a stirring solution of the product from step (a) (21.4g) in acetonitrile (250ml) at 0°C was added potassium nitrate (25.2g), followed by sulfuryl chloride (33.75g) over a 10 min period. The reaction mixture was allowed to warm to RT over a 2 h period, then partitioned between ether and water. The etheral layer

was extracted 3 times with water, dried and concentrated to give the desired product (27 g)

$C_{13}H_9ClO_3S$ x (0.67 H_2O): C, 53.33; H, 3.56; Cl, 12.11; S, 10.95.

Found: C, 53.43; H, 3.27; Cl, 12.03; S, 11.06.

(c) 2-Amino-2-ethylhexanol

To the product of Synthetic Example 1(d) (46.7g) was added at RT over a 2 h period LAH (1M in THF, 375ml). After 24 h, the reaction mixture was quenched by careful addition of 400 ml aqueous 1N NaOH. The reaction was extracted with diethyl ether. The ether layer was dried, filtered and concentrated to give the desired product as a viscous colorless oil, (38.7g).

^1H NMR (DMSO-d_6) d 0.81 (t, 3H); 0.88 (t, 3H); 1.17-1.40 (m, 8H); 3.17 (m, 2H); 4.40 (br, 1H); 3.30-3.50 (br, 2H) overlaps water peak.

(d) 2-Benzoyl-N-(1-ethyl-1-hydroxymethyl-pentyl) benzene-sulfonamide

To a stirring solution of the product from step (c) (14.5g) and triethylamine (10.1g) in THF at RT was added a 25 ml THF solution of the product from (b) (27 g). After 16 h the reaction mixture was partitioned between ethyl ether and 1.0 N HCl, dried, concentrated to give the desired product as a viscous yellow oil (31.08g).

Calcd. for $C_{21}H_{27}NO_4S$ x (0.33 H_2O): C, 63.77; H, 7.05; N, 3.54; S, 8.11.

Found: C, 63.89; H, 7.07; N, 3.59; S, 8.05.

(e) 2-Benzoyl-N-(1-ethyl-1-formyl-pentyl)-benzenesulfonamide

To a stirring solution of the product from step (d) (31.08g) in methylene chloride (300ml) was added pyridinium chlorochromate (17.2g) . After 16 h the reaction mixture was filtered through 50g Florisil® pad, concentrated and chromatographed (25% ethyl acetate/ hexane) to give the desired product as an off-white solid (20.5g)

^1H NMR (DMSO-d_6) d 0.50 (t, 3H); 0.60 (t, 3H); 0.65-1.00 (m, 4H); 1.20 (m, 1H); 1.45 (m, 1H); 1.63 (m, 2H); 7.23-7.80 (m, 9H); 8.04 (d, 1H); 9.13 (s, 1H).

(f) 7-Ethyl-9-phenyl-7-butyl-6,7-dihydro-5-thia-6-aza-benzocycloheptene-5,5-dioxide

A mixture of titanium trichloride (30.1g) and 1, 2-dimethoxyethane (350ml) was refluxed for 16 h. Zn-Cu couple (50.1g) was added, and the reaction mixture was refluxed 2h at which point a solution of the product from step (e) in DME (40 ml) was added using syringe pump (8.0g) at a rate of 4ml/hr. Refluxing was continued for another 12 h. The reaction was allowed to come to RT, filtered through 50 g Florisil® pad, and concentrated to give the desired product (4.49g)
Calcd for $C_{21}H_{25}NO_2S$: C, 70.95; H, 7.09; N, 3.94; S, 9.02.
Found: C, 70.66; H, 7.13; N, 3.81; S, 8.88.

(g) (±)-Trans-7-Ethyl-9-phenyl-7-butyl-6,7,8,9-tetrahydro-5-thia-6-aza-benzocycloheptane-5,5-dioxide

A 50ml absolute ethanol solution of the product from step (f) under 40 p.s.i hydrogen pressure on a Parr® hydrogenation apparatus was agitated at RT with 20% $Pd(OH)_2$ (0.20g) for 18 h at RT. The reaction mixture was removed to a nitrogen atmosphere, filtered through Celite® (diatomaceous earth) and concentrated. Column chromatography gave the desired product as the trans isomer (50mg).
MS Da/e = 341 (M -16)
Calcd for $C_{21}H_{27}NO_2S$ x (0.25 H2O): C, 69.67; H, 7.66; N, 3.87; S, 8.86.
Found: C, 69.66; H, 7.70; N, 3.79; S, 8.79.

Synthetic Example 10

Preparation of (±)-3-Butyl-3-ethyl-2,3-dihydro-8-methoxy-5-phenyl-5H-1,4-benzothioxepine

(a) O-(2-benzoyl-5-methoxyphenyl)-dimethylthiocarbamate

To a solution of 2-hydroxy-4-methoxybenzophenone (100 g) in dioxane (500 ml), triethylamine (122 ml), and dimethylamino pyridine (5.0 g), was added dropwise dimethylthiocarbamoyl chloride (56.9 g) dissolved in dioxane (200 ml). The reaction mixture was refluxed 18h, allowed to cool and diluted with 500 ml water and extracted with ethyl acetate. The organic extracts were dried and the solvents evaporated. The product was crystallized from ether/hexane and dried giving the desired product (105.6 g).
Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44; S, 10.17
Found: C, 64.66; H, 5.39; N, 4.48; S, 10.13.

(b) S-(2-benzoyl-5-methoxyphenyl)dimethylthiocarbamate

A suspension of the product from step (a) (97.4 g) in tetradecane (500 ml) was stirred at 255 °C for 30 min. The reaction mixture was cooled, diluted with 2 volumes of petroleum ether and loaded onto a silica gel column. The product was eluted with 40% ethyl acetate/petroleum ether giving the desired product (65.0 g).

Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44; S, 10.17.

Found: C, 64.59; H, 5.39; N, 4.43; S, 10.24.

(c) (±)-2-Butyl-2-ethyl-oxirane

To a solution of trimethylsulfoxonium iodide (86.8g) in DMSO (650ml) was added sodium hydride (15.8 g, 60% in mineral oil) and the mixture stirred 15 min. To the resulting ylide was added dropwise 3-heptanone (30.0 g) dissolved in 60 ml DMSO, and the reaction was heated to 50 °C for 2h. The reaction was cooled, diluted with water (400 ml) and extracted with ether. The organic extracts were dried (Na_2SO_4) and concentrated. The product was distilled at atmospheric pressure to give the desired compound (15.36 g)

MS Da/e = 111 ($M(-H_2O)H^+$).

(d) (±)-2-((2-Ethyl-2-hydroxyhexyl)thio)-4-methoxybenzophenone

To a solution of the product from step (b) (10.0 g) in THF (50 ml) was added KOH (100 ml, 0.6 M in MeOH) and the mixture stirred 90 min in a 50 °C water bath. The reaction mixture was acidified with 1 N HCl, extracted with ether, dried and concentrated. To the resulting yellow oil was added tetrabutylammonium fluoride (3.2 ml, 1M in THF) and the epoxide from step (c) (4.50 g). The reaction was stirred overnight at RT. The reaction mixture was neutralized with 1 N HCl, extracted with ether, dried (Na_2SO_4) and concentrated. Column chromatography (15% ethyl acetate/petroleum ether) gave the desired product (11.56 g).

MS Da/e = 395($M+ Na^+$)

(e) (±)-Alpha-(2-((2-Ethyl-2-hydroxyhexyl)thio)-4-methoxy)phenyl-benzyl alcohol

To a solution of the product of step (d) (10.2 g) in methanol (125 ml) at 0 °C was added sodium borohydride (2.08 g) in 4 portions. After stirring at RT for 30

min, the reduction was complete. The reaction mixture was neutralized with 1 N HCl, extracted with ethyl acetate, dried and concentrated. Column chromatography (15% ethyl acetate/petroleum ether) gave the desired product (9.93 g).

MS Da/e = 397 ($M+ Na^+$)

(f) (±)-3-Butyl-3-ethyl-2,3-dihydro-8-methoxy-5-phenyl-5H-1,4-benzothioxepine

To a solution of the product from step (e) (4.19 g) in toluene (25 ml) were added Nafion® NR50 beads (0.2 g). The mixture was refluxed 10 min. The beads were recovered in a sintered glass filter and the toluene was removed on a rotary evaporator. Column chromatography (2% ethyl acetate/petroleum ether) gave the desired product (3.78 g) as a 1:1 mixture of isomers.

MS Da/e = 229 (M - 127).

Calcd for $C_{22}H_{28}O_2S$: C, 74.12; H, 7.92; S, 8.99.

Found: C, 74.17; H, 7.91; S, 9.06.

Synthetic Example 11

Preparation of (±)-3-Butyl-3-ethyl-2,3-dihydro-8-methoxy-5-phenyl-5H-1,4-benzothioxepine

Repeated chromatography of the product from Synthetic Example 10 (f) using toluene as eluant gave a partial separation of isomers and 1.21 g of the desired product whose configuration was confirmed by nOesy spectroscopy.

^1H NMR (DMSO-d_6) d 7.37(m, 5H); 7.01 (d, 1H); 6.60 (dd, 1H); 6.20 (m, 2H); 3.68 (s, 3H); 3.17 (d, 1H); 2.70 (d, 1H); 2.01 (m, 1H); 1.58 (m, 3H); 1.16 (m, 4H); 0.79 (t, 3H); 0.70 (t, 3H).

MS Da/e = 229 (M-127).

Synthetic Example 12

Preparation of (±)-3,3-Diethyl-2,3-dihydro-8-methoxy-5-phenyl-5H-1,4-benzothioxepine

(a) 2,2-Diethyl-oxirane

To a solution of trimethylsulfoxonium iodide (48.4 g) in DMSO (300ml) was added in 4 portions sodium hydride (8.8 g, 60% in mineral oil) and the mixture

stirred 30 min. To the resulting ylide was added dropwise 2-pentanone (30.0 g) dissolved in 50 ml DMSO, and the reaction was heated to 50 °C for 1h. The reaction was cooled, diluted with water (200 ml) and extracted with ether. The organic extracts were dried (Na_2SO_4) and concentrated. The product was distilled at atmospheric pressure (bp = 100-102 °C) to give the desired product (11.50 g).

^1H NMR (DMSO-d_6) d 2.50 (m, 2H); 1.52 (m, 4H); 0.82 (t, 6H).

(b) 2-((2-Ethyl-2-hydroxybutyl)thio)-4-methoxybenzophenone

To a solution of the product from Synthetic Example 10(b) (18.0 g) in THF (90ml) was added KOH (180 ml, 0.6 M in MeOH) and the mixture stirred 90 min in a 50 °C water bath. The reaction mixture was acidified with 1 N HCl, extracted ether, dried and concentrated. To the resulting yellow oil was added tetrabutylammonium fluoride (7.7 ml, 1M in THF) and epoxide product from step (a) (9.5 g). The reaction was stirred overnight at RT. The reaction mixture was neutralized with 1 N HCl, extracted ether, dried (Na_2SO_4) and concentrated. Column chromatography (15% ethyl acetate/petroleum ether) gave the desired product (16.51g).

Calcd for $C_{20}H_{24}O_3S$: C, 69.73; H, 7.02; S, 9.30.

Found: C, 69.85; H, 6.99; S, 9.39.

(c) (±)-Alpha-(2-((2-Ethyl-2-hydroxybutyl)thio)-4-methoxy)phenyl-benzyl alcohol

To a solution of the product from step (b) (14.2 g) in methanol (200 ml) at 0 °C was added sodium borohydride (3.08 g) in 3 portions. After stirring at RT for 1 h, the reduction was complete. The reaction mixture was neutralized with 1 N HCl, extracted with ethyl acetate, dried and concentrated. Column chromatography (15% ethyl acetate/petroleum ether) gave the desired product (13.66 g).

Calcd for $C_{20}H_{26}O_3S$: C, 69.33; H, 7.56; S, 9.25.

Found: C, 69.31; H, 7.61; S, 9.23.

(d) (±)-3,3-Diethyl-2,3-dihydro-8-methoxy-5-phenyl-5H-1,4-benzothioxepine

To a solution of the product from step (c) (12.8 g) in toluene (100 ml) were added Nafion® NR50 beads (0.8 g). The mixture was refluxed for 20 min. The beads were recovered in a sintered glass filter and the toluene was removed on a rotary evaporator. Column chromatography (10% ethyl acetate/petroleum ether) gave the desired product (10.63 g).

MS Da/e = 351 ($M + Na^+$).

Calcd for $C_{20}H_{24}O_2S$: C, 73.13; H, 7.05; S, 9.76.

Found: C, 73.19; H, 7.36; S, 9.86.

Synthetic Example 13

Preparation of (±)-3-Butyl-3-ethyl-2,3-dihydro-8-methoxy-5-phenyl-5H-1,4-benzothioxepine 1,1-dioxide

To a solution of the product from Synthetic Example 10 (f) (3.33 g) in THF (60 ml) and t-butanol (21 ml) was added 4-methyl-morpholine-N-oxide (3.28 g) and osmium tetroxide (6.0 ml, 2.5 wt% solution in 2-methyl-2-propanol), and the solution was stirred 18 h at room temperature. The reaction mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography (10% ethyl acetate/petroleum ether) gave the desired product (3.02 g) as a 1:1 mixture of isomers.

MS Da/e = 411 ($M + Na^+$).

Calcd for $C_{22}H_{28}O_4S$: C, 68.01; H, 7.26; S, 8.25.

Found: C, 68.18; H, 7.32; S, 8.16.

Synthetic Example 14

Preparation of (±)-3,3-Diethyl-2,3-dihydro-8-methoxy-5-phenyl-5H-1,4-benzothioxepine 1,1-dioxide

To a solution of the product from Synthetic Example 12 (d) (10.04 g) in t-butanol (45 ml) was added 4-methyl-morpholine-N-oxide (10.5 g) and osmium tetroxide (6.0 ml, 2.5 wt% solution in 2-methyl-2-propanol), and the solution was stirred 18 h at room temperature. The reaction mixture was diluted with water (100 ml) and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography (20% ethyl acetate/petroleum ether) gave the desired product (9.63 g).

MS Da/e = 383 ($M + Na^+$).

Calcd for $C_{20}H_{24}O_4S$: C, 66.64; H, 6.71; S, 8.89.

Found: C, 66.72; H, 6.74; S, 8.95.

Synthetic Example 15

Preparation of (±)-Trans-3-butyl-3-ethyl-2,3-dihydro-8-methoxy-5-phenyl-5H-1,4-benzothioxepine 1,1-dioxide

To a solution of the product from Synthetic Example 11 (1.16 g) in THF (20 ml) and t-butanol (7 ml) was added 4-methyl-morpholine-N-oxide (1.14 g) and osmium tetroxide (2.0 ml, 2.5 wt% solution in 2-methyl-2-propanol), and the solution was stirred 18h at room temperature. The reaction mixture was partitioned between water and ethyl acetate and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography (15% ethyl acetate/petroleum ether) gave the desired product (1.21 g).

MS Da/e = 411 ($M + Na^+$).

Calcd for $C_{22}H_{28}O_4S$: C, 68.01; H, 7.26; S, 8.25.

Found: C, 67.83; H, 7.41; S, 8.19.

Synthetic Example 16

Preparation of 3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-bromo-8-hydroxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide

(a) Bis-2,4-dibromo-5-methoxy disulfide

Bromine (57.6 g) was added to a methanol solution (150 ml) of 3-methoxybenzenethiol (25 g) at 0 °C and the mixture was stirred at room temperature for 24 h. The reaction was concentrated, diluted with ethyl acetate, extracted with water, dried and concentrated. The residue was dissolved in acetic acid and treated with bromine (16 g) for 30 min. A tan solid was filtered from the reaction and triturated with methylene chloride to give the title compound as an off-white powder (9.9 g).

^1H NMR ($CDCl_3$) d 3.60 (s, 6H); 7.18 (s, 2H); 7.64 (s, 2H).

(b) 2,4-Dibromo-5-methoxybenzenesulfonyl chloride

Sulfuryl chloride (19.6 g) was added to a stirring mixture of Bis-2,4-dibromo-5-methoxy disulfide (17.5 g) and potassium nitrate (14.6 g) in acetonitrile (200 ml) at RT. After 24 h the mixture was diluted with ice/ether, extracted with cold

water, dried, concentrated to give the title compound as an off-white solid (16.2 g).

Calcd for $C_7H_5Br_2ClO_3S$: C, 23.07; H, 1.38; S, 8.80. Found: C, 22.82; H, 1.40; S, 8.68.

(c) 2,4-Dibromo-5-methoxy-N-[1-ethyl-1-(phenylamino-methyl)-pentyl]-benzenesulfonamide

2, 4-Dibromo-5-methoxybenzenesulfonyl chloride (8.0 g) in THF (40 ml) was added to a mixture of triethylamine (3.02 g) and 2-ethyl-N-1-phenyl-hexane-1,2-diamine (6.00 g) and stirred at room temperature for 24 h. The reaction mixture was diluted with ethyl acetate, extracted with water, dried, filtered, concentrated. The residue was chromatographed on silica gel (EtOAc:Hexane/1:4) to give the title compound as a nearly colorless oil (0.85 g).

^1H NMR (DMSO-d6) d 0.72 (t, 6H); 1.02 (m, 4H); 1.53 (m, 2H); 1.60 (m, 2H); 3.00 (m, 2H); 3.80 (s, 3H); 4.80 (m, 1H); 6.47-6.50 (m, 3H); 7.00 (t, 2H); 7.50 (s, 1H); 7.58 (s, 1H); 7.99 (s, 1H).

(d) 3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-bromo-8-methoxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide

2,5-Dibromo-N-[1-ethyl-1-(phenylamino-methyl)-pentyl]-benzenesulfonamide (0.85 g) in dimethylformamide (40 ml) , copper metal (50 mg) and potassium carbonate (0.41 g) was refluxed for 24 h. The reaction mixture was cooled to room temperature and diluted with ether, extracted with water, filtered through Florisil®, concentrated and chromatographed on silica gel (EtOAc:Hexane/1:4) to give the title compound as a tan powder (0.38 g).

Calcd for $C_{21}H_{27}BrN_2O_3S$: C, 53.96; H, 5.82; N, 5.99; Br, 17.10; S, 6.86.
Found: C, 54.08; H, 5.93; N, 6.04; Br, 17.20; S, 6.75.

(e) 3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-bromo-8-hydroxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide

1molar BBr_3 in CH_2Cl_2 (60 ml) was added to 3-butyl-3-ethyl-2,3,4,5-tetrahydro-7-bromo-8-methoxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide (4.67g) in methylene chloride (20 ml) at 0 °C and the mixture was stirred at RT for 24 h. Reaction was partitioned between aq. NaHCO3 and CH_2Cl_2 and extracted with CH_2Cl_2. The organic phase was dried, filtered, concentrated and

chromatographed on silica gel (EtOAc:Hexane/1:2) to give the title compound as a tan solid (1.7 g).

^{1}H NMR (DMSO-d6) d 0.68 (m, 6H); 0.84-1.08 (m, 4H); 1.20-1.70 (m, 4H); 3.58-3.90 (m, 2H); 6.95 (m, 2H); 7.02 (d, 2H); 7.23 (m, 3H); 7.38 (s, 1H).

Calcd for $C_{20}H_{25}BrN_2O_3S$ 0.6 H_2O: C, 51.74; H, 5.69; N, 6.03; Br, 17.21; S, 6.91. Found: C, 52.09; H, 5.74; N, 5.54; Br, 17.45; S, 6.55.

Synthetic Example 17

Preparation of 3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-methoxy-8-hydroxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide

The product from Synthetic Example 16, 3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-bromo-8-methoxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide (1.7 g), and copper (I) bromide (120mg) was refluxed for 90 min in 25% NaOMe/MeOH (12 ml) and ethyl acetate (0.1 ml). The reaction mixture was cooled to RT, diluted with ether, filtered through Florisil®, triturated with acetic acid, dried and chromatographed on silica gel (EtOAc:Hexane/1:2) to give the title compound as an amber gum (0.33 g).

^{1}H NMR (DMSO-d6) d 0.68 (m, 6H); 0.84-1.08 (m, 4H); 1.20-1.70 (m, 4H); 3.57 (s, 3H); 3.58-3.90 (m, 2H); 6.40 (s, 1H); 6.80 (t, 1H); 6.99 (m, 3H); 7.19 (s, 1H); 7.21 (t, 2H); 9.40 (s, 1H).

Calcd for $C_{20}H_{25}BrN_2O_3S$ 0.75 H_2O 0.5 HOAc: C, 58.97; H, 6.86; N, 6.25; S, 7.16.

Found: C, 59.03; H, 6.71; N, 6.15; S, 6.97.

Biological Testing

Bile Acid Transport Inhibitor Assay

The human ileal bile acid transporter (HIBAT) was stabley expressed in Chinese Hamster Ovary Cells (CHO cells). The cells were plated at a density of 50,000 cells/well in a 24 well format, and cultured for 48-72 hours at 37° C. and 5%CO_2. Cell were washed twice in Hanks Balanced Salt Solution, buffered to pH 7.4 with Hepes-Tris (HBSSH). At t=0 minutes, cells were incubated with 0.2 mL of incubation medium containing 0.5 uM taurocholate, 0.5 uCi/mL [3H]-taurocholate, plus or minus inhibitors, at 37° C. Cells were then returned to the CO_2 incubator. The assay was terminated at t=10 minutes, when the plate is placed into an ice-water bath. Radiolabeled compound was aspirated, and the cells were washed three times with HBSSH containing 1 mM taurocholate at 4° C. Excess liquid was blotted away and the cells were lysed with 0.1N NaOH. Cell associated radioactivity was determined by liquid scintillation counting. Total cell protein was measured using a Bio-Rad protein assay. The IC_{50} was determined by a plot of the % Control Activity versus log[I].

TABLE 1 Inhibition of Human Bile Acid Transport

Compound of Example	% Inhibition at 10 micromolar
1	41
3	41
4	37
6	89
7	30
9	45
14	26
15	46
16	15
17	57

Pharmaceutical Composition Examples

In the following Examples, the active compound can be any compound of formula (I) and/or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

(I) Tablet compositions

The following compositions A and B can be prepared by wet granulation of ingredients (a) to (c) and (a) to (d) with a solution of povidone, followed by addition of the magnesium stearate and compression.

Composition A

		mg/tablet	mg/tablet
(a)	Active ingredient	250	250
(b)	Lactose B.P.	210	26
(c)	Sodium Starch Glycollate	20	12
(d)	Povidone B.P.	15	9
(e)	Magnesium Stearate	5	3
		500	300

Composition B

		mg/tablet	mg/tablet
(a)	Active ingredient	250	250
(b)	Lactose 150	150	-
(c)	Avicel PH 101	60	26
(d)	Sodium Starch Glycollate	20	12
(e)	Povidone B.P.	15	9
(f)	Magnesium Stearate	5	3
		500	300

Composition C

	mg/tablet
Active ingredient	100
Lactose	200
Starch	50
Povidone	5
Magnesium Stearate	4
	359

The following compositions D and E can be prepared by direct compression of the admixed ingredients. The lactose used in composition E is of the direct compression type.

Composition D

	mg/tablet
Active ingredient	250
Magnesium Stearate	4
Pregelatinised Starch NF15	146
	400

Composition E

	mg/tablet
Active ingredient	250
Magnesium Stearate	5
Lactose	145
Avicel	100
	500

Composition F (Controlled release composition)

		mg/tablet
(a)	Active ingredient	500
(b)	Hydroxypropylmethylcellulose Methocel K4M Premium)	112
(c)	Lactose B.P.	53
(d)	Povidone B.P.C.	28
(e)	Magnesium Stearate	7

The composition can be prepared by wet granulation of ingredients (a) to (c) with a solution of povidone, followed by addition of the magnesium stearate and compression.

Composition G (Enteric-coated tablet)

Enteric-coated tablets of Composition C can be prepared by coating the tablets with 25mg/tablet of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethyl- cellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

Composition H (Enteric-coated controlled release tablet)

Enteric-coated tablets of Composition F can be prepared by coating the tablets with 50mg/tablet of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethyl- cellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

(ii) Capsule compositions

Composition A

Capsules can be prepared by admixing the ingredients of Composition D above and filling two-part hard gelatin capsules with the resulting mixture. Composition B (infra) may be prepared in a similar manner.

Composition B

		mg/capsule
(a)	Active ingredient	250
(b)	Lactose B.P.	143
(c)	Sodium Starch Glycollate	25
(d)	Magnesium Stearate	2
		420

Composition C

		mg/capsule
(a)	Active ingredient	250
(b)	Macrogol 4000 BP	350
		600

Capsules can be prepared by melting the Macrogol 4000 BP, dispersing the active ingredient in the melt and filling two-part hard gelatin capsules therewith.

Composition D

	mg/capsule
Active ingredient	250
Lecithin	100
Arachis Oil	100
	450

Capsules can be prepared by dispersing the active ingredient in the lecithin and arachis oil and filling soft, elastic gelatin capsules with the dispersion.

Composition E (Controlled release capsule)

		mg/capsule
(a)	Active ingredient	250
(b)	Microcrystalline Cellulose	125
(c)	Lactose BP	125
(d)	Ethyl Cellulose	13
		513

The controlled release capsule composition can be prepared by extruding mixed ingredients (a) to (c) using an extruder, then spheronising and drying the extrudate. The dried pellets are coated with a release controlling membrane (d) and filled into two-part, hard gelatin capsules.

Composition F (Enteric capsule)

		mg/capsule
(a)	Active ingredient	250
(b)	Microcrystalline Cellulose	125
(c)	Lactose BP	125
(d)	Cellulose Acetate Phthalate	50
(e)	Diethyl Phthalate	5
		555

The enteric capsule composition can be prepared by extruding mixed ingredients (a) to (c) using an extruder, then spheronising and drying the extrudate. The dried pellets are coated with an enteric membrane (d) containing a plasticizer (e) and filled into two-part, hard gelatin capsules.

Composition G (Enteric-coated controlled release capsule)

Enteric capsules of Composition E can be prepared by coating the controlled-release pellets with 50mg/capsule of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

(iii) Intravenous injection composition

Active ingredient	0.200g
Sterile, pyrogen-free phosphate buffer (pH 9.0) to	10 ml

The active ingredient is dissolved in most of the phosphate buffer at 35-40°C, then made up to volume and filtered through a sterile micropore filter into sterile 10 ml glass vials (Type 1) which are sealed with sterile closures and overseals.

(iv) Intramuscular injection composition

Active ingredient	0.20 g
Benzyl Alcohol	0.10 g
Glycofurol 75	1.45 g
Water for Injection q.s. to	3.00 ml

The active ingredient is dissolved in the glycofurol. The benzyl alcohol is then added and dissolved, and water added to 3 ml. The mixture is then filtered through a sterile micropore filter and sealed in sterile 3 ml glass vials (Type 1).

(v) Syrup composition

Active ingredient	0.25g
Sorbitol Solution	1.50g
Glycerol	1.00g
Sodium Benzoate	0.005g
Flavour	0.0125ml
Purified Water q.s. to	5.0ml

The sodium benzoate is dissolved in a portion of the purified water and the sorbitol solution added. The active ingredient is added and dissolved. The resulting solution is mixed with the glycerol and then made up to the required volume with the purified water.

(vi) Suppository composition

	mg/suppository
Active ingredient	250
Hard Fat, BP (Witepsol H15 - Dynamit NoBel)	1770

One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200lm sieve and added to the molten base with mixing, using a Silverson fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining Witepsol H15 is added to the suspension which is stirred to ensure a homogenous mix. The entire suspension is then passed through a 250lm stainless steel screen and, with continuous stirring, allowed to cool to 40°C. At a temperature of 38-40°C, 2.02g aliquots of the mixture are filled into suitable plastic moulds and the suppositories allowed to cool to room temperature.

(vii) Pessary composition

	mg/pessary
Active ingredient (63lm)	250
Anhydrous Dextrose	380
Potato Starch	363
Magnesium Stearate	7
	1000

The above ingredients are mixed directly and pessaries prepared by compression of the resulting mixture.

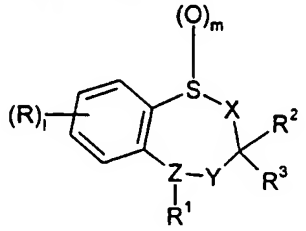
(viii) Transdermal composition

Active ingredient	200mg
Alcohol USP	0.1ml
Hydroxyethyl cellulose	

The active ingredient and alcohol USP are gelled with hydroxyethyl cellulose and packed in a transdermal device with a surface area of 10 cm^2.

CLAIMS

1. A compound of formula (I)



(I)

wherein :

l is an integer of from 1 to 4;

m is an integer of from 0 to 2;

R is independently selected from hydrogen, halogen, nitro, hydroxy, phenylalkoxy, C_{1-4} alkoxy, C_{1-6} alkyl, $-SO_3R''$, $-CO_2R''$ and $-O(CH_2)_pSO_3R''$ wherein p is an integer of from 1 to 4 and R'' is hydrogen or C_{1-6} alkyl, wherein said phenylalkoxy, alkoxy and alkyl groups are optionally substituted by one or more halogen atoms;

R^1 is phenyl or pyridyl optionally substituted by one to five groups independently selected from halogen, nitro, hydroxy, phenylalkoxy, C_{1-4} alkoxy, C_{1-6} alkyl, $-SO_3R'''$, $-CO_2R'''$ and $-O(CH_2)_pSO_3R'''$ wherein p is an integer of from 1 to 4 and R''' is hydrogen or C_{1-6} alkyl, wherein said phenylalkoxy, alkoxy and alkyl groups are optionally substituted by one or more halogen atoms;

R^2 is a group independently selected from C_{1-6} alkyl (including cycloalkyl and cycloalkylalkyl), C_{2-6} alkenyl, and C_{2-6} alkynyl which groups are optionally substituted by one or more groups or atoms independently selected from halogen, oxo, C_{1-4} alkoxy, hydroxy, amino optionally substituted by C_{1-6} alkyl, thio, and C_{1-6} alkylthio;

R^3 is a group independently selected from C_{1-6} alkyl (including cycloalkyl and cycloalkylalkyl), C_{2-6} alkenyl, and C_{2-6} alkynyl which groups are optionally substituted by one or more groups or atoms independently selected from halogen, oxo, C_{1-4} alkoxy, hydroxy, amino optionally substituted by C_{1-6} alkyl, thio, and C_{1-6} alkylthio;

X is CH_2 or NH;

Y is CH_2 or O; and

Z is CH or N;

provided that when X is CH_2, Y is O;
and pharmaceutically acceptable derivatives or solvates thereof.

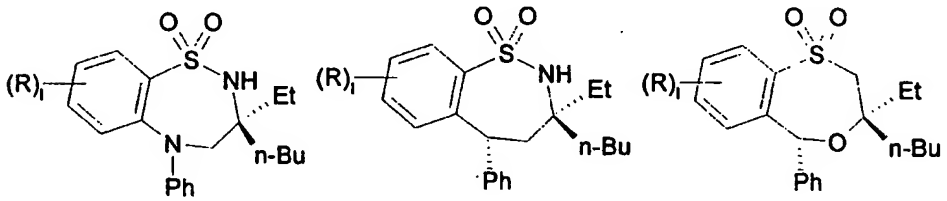
2. A compound according to Claim 1 wherein l is 1 or 2 and R is hydrogen, bromo, hydroxy, methoxy or a combination thereof.

3. A compound according to Claim 1 or 2 wherein R^1 is unsubstituted phenyl.

4. A compound according to any of Claims 1-3 wherein R^2 is ethyl and R^3 is n-butyl.

5. A compound according to any Claims 1-4 wherein X is NH, Y is CH_2 and Z is CH or N.

6. A compound represented by formula (1d), (1e) or (1f)



(Id) (Ie) (If)

wherein
l is an integer of from 1 to 4; and
R is independently selected from hydrogen, halogen, nitro, hydroxy, phenylalkoxy, C_{1-4} alkoxy, C_{1-6} alkyl, $-SO_3R''$, $-CO_2R''$ and $-O(CH_2)_pSO_3R''$ wherein p is an integer of from 1 to 4 and R" is hydrogen or C_{1-6} alkyl, wherein said phenylalkoxy, alkoxy and alkyl groups are optionally substituted by one or more halogen atoms;
and pharmaceutically acceptable derivatives or solvates thereof.

7. A compound selected from:
(3S)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;

(3S)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-8-bromo-5-phenyl-1,2,5-benzothiadiazepine 1,1- dioxide;
(3S)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
(3S)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-8-hydroxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
(3S)-3-Butyl-3-Ethyl-2,3,4,5-Tetrahydro-7,8-Dichloro-5-phenyl-1,2,5 Benzothiadiazepine 1,1-dioxide;
(3S)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
(3S)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7,8-dihydroxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
(3S)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-hydroxy-8-methoxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
(7S,9R)-7-Ethyl-9-phenyl-7-butyl-6,7,8,9-tetrahydro-5-thia-6-aza-benzocycloheptane 5,5-dioxide;
(3R,5R)-3-Butyl-3-ethyl-2,3-dihydro-8-methoxy-5-phenyl-5H-1,4-benzothioxepine 1,1-dioxide;
(5R)-3,3-Diethyl-2,3-dihydro-8-methoxy-5-phenyl-5H-1,4-benzothioxepine1,1-dioxide;
(3S)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-bromo-8-hydroxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
(3S)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-methoxy-8-hydroxy-5-phenyl-1,2,5-benzothiadiazepine 1,1-dioxide;
or a pharmaceutically acceptable derivative thereof.

8. A method of treating a clinical condition in a mammal for which a bile acid uptake inhibitor is indicated which comprises, administering to a mammal an effective bile acid uptake inhibition amount of a compound according to any one of claims 1-7.

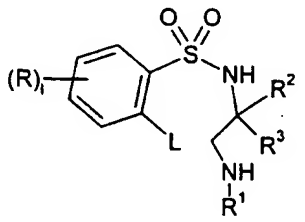
9. A pharmaceutical composition comprising a compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, at least one pharmaceutically acceptable carrier, and optionally one or more other physiologically active agents.

10. A compound according to any one of Claims 1 to 7 or a pharmaceutically acceptable salt, solvate, or physiologically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy.

11. Use of a compound according to any one of Claims 1 to 7 or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a bile uptake inhibitor is indicated.

12. A process for the preparation of a compound according to Claim 1, or a salt, solvate or physiologically functional derivative thereof; which comprises:

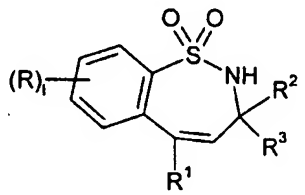
(a) wherein X is NH, Y is CH_2, Z is N, and m is 2 by cyclization of compounds of formula (II):



(II)

wherein L is a suitable leaving group, or

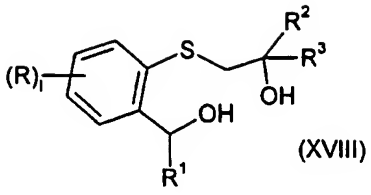
(b) wherein X is NH, Y is CH_2, Z is CH_2 and n is 2 by reduction of the olefinic bond of compounds of formula (X):



(X)

or

(c) wherein X and Z are CH_2, Y is O, and m is 0 by cyclization of compounds of formula (XVIII):



(XVIII)

or

(d) by conversion of a different compound according to Claim 1 by standard methods.

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/EP 98/01078

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D285/36 C07D281/02 C07D327/02 C07D291/08 C07D417/04
C07D411/04 C07D419/04 A61K31/55 A61K31/39

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 08484 A (MONSANTO COMPANY) 21 March 1996 cited in the application see the whole document ---	1-12
A	WO 93 16055 A (THE WELLCOME FOUNDATION LIMITED) 19 August 1993 cited in the application see the whole document ---	1-12
A	WO 96 05188 A (THE WELLCOME FOUNDATION LIMITED) 22 February 1996 cited in the application see the whole document --- -/--	1-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 June 1998	22. 06. 98

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. .tional Application No
PCT/EP 98/01078

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 16051 A (THE WELLCOME FOUNDATION LIMITED) 30 May 1996 cited in the application see the whole document	1-12

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/01078

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 8
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 8 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/EP 98/01078

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